Patent
Attorney's Docket No. 002010-586

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Jing WU et al.	)	Group Art Unit: 1624
	)	
Application No.: 09/916,440	)	Examiner: B. Kifle
	)	
Filed: July 30, 2001	)	Confirmation No.: 2003
	)	
For: CYCLOALKYL, LACTAM, LACTONE AND RELATED COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, AND METHODS FOR INHIBITING β-AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS	)	

APPEAL BRIEF TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This appeal is from the decision of the Primary Examiner dated December 20, 2002 (Paper No. 13), finally rejecting claims 91-95, 104, 109-122, 131 and 136-145. Claims 91 and 118 are reproduced in Appendix A to this brief.

A check covering the [ ] $160.00 (2402) [X] $320.00 (1402) Government fee and two extra copies of this brief are being filed herewith.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in triplicate.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____ #51,147
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Date: March 31, 2003

#16

Patent
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In re Patent Application of	
Jing Wu, et al.	Group Art Unit: 1624
Application No.: 09/916,440	Examiner: B. Kifle
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For: CYCLOALKYL, LACTAM, LACTONE AND RELATED COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, AND METHODS FOR INHIBITING β-AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS	**APPEAL NO. 1**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPELLANTS' BRIEF

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* These claims assume entry of the Amendment After Final Rejection Pursuant to 37 C.F.R. § 1.116(b). That is, the word "optionally" has been deleted from a portion of the description of the variable "W."

** So that these claims mirror Claims 91 and 118 from Appendix A (other than containing the substituent definitions), the word "optionally" has also been deleted from a portion of the description of the variable "W" in these claims.

I. REAL PARTY IN INTEREST

The assignment filed in the parent to this case (USSN 08/996,422; Attorney's Docket No. 002010-062 ("the -062 case")) is to both Eli Lilly and Company and Athena Neurosciences, Inc. Subsequent to this assignment, Athena Neurosciences, Inc. was purchased by Elan Pharmaceuticals, Inc. Accordingly, the real parties in interest for the involved application are Eli Lilly and Company and Elan Pharmaceuticals, Inc.

II. RELATED APPEALS AND INTERFERENCES

This appeal pertains to U.S. Patent Application Serial No. 09/915,440; Attorney Docket No.: 002010-586 ("the -586 case"). A companion appeal brief pertaining to U.S. Patent Application Serial No. 09/915,263; Attorney Docket No.: 002010-593 ("the -593 case") is expected to be filed on or before April 28, 2003.[1]

The appealed claims in this application are directed to compounds and pharmaceutical compositions, whereas the claims to be appealed in the -593 case are directed to methods using these compounds and pharmaceutical compositions. As the -586 case and the -593 case are directed to different statutory classes, Appellants submit there are no related appeals or interferences.

Other than the foregoing, there are no other appeals or interferences known to Appellants, their legal representatives, or their assignees which will directly affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

[1] The -593 case is a divisional of the -062 case. Claims in the -593 case have also been finally rejected as containing an improper Markush group.

III. STATUS OF CLAIMS

This application is a divisional of U.S. Patent Application Serial No. 08/996,422; Attorney's Docket No. 002010-062.[2] The status of the claims in this application is as follows: Claims 1-90 have been canceled; Claims 91-145 are pending; Claims 96-103, 105-108, 123-130, and 132-135 have been withdrawn from consideration; Claims 92-95, 104, 109-117, 119-122, 131, and 136-145 are being canceled by the concurrently-filed Amendment After Final Rejection; and Claims 91 and 118 are being appealed. *See Appendices A[3] and B.*[4]

Claims 91 and 118 stand finally rejected:

> as being drawn to an improper Markush group, that is, the claims lack unity of invention. The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference. *See Appendix E, Pages 2-5.*

In the previous office action, the Examiner rejected the same claims:

> under a judicially created doctrine as being drawn to an improper Markush group, that is, the claims lack unity of invention. The ring formed by W, together with -$C(H)_pC(=X)$ ... are defined in such a way that they keep changing the core

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[2] A restriction requirement issued in the -062 case between its method claims (Claims 1-31) and its compound/composition claims (Claims 32-90). Method claims were elected in the -062 case. The -062 case was allowed on December 27, 2002, and its Issue Fee was paid on March 10, 2003. The -062 case has yet to issue as a patent.

[3] Claims 91 and 118 as contained in Appendix A assume entry of Appellants' concurrently-filed Amendment After Final Rejection Pursuant To 37 C.F.R. § 1.116(b). That is, the word "optionally" has been removed at one location in the description of W.

[4] For the convenience of the Board, Appellants have attached, as Appendix B, a redacted version of Claims 91 and 118 which contain the content of pending Claims 91 and 118, but do not contain the lengthy substituent definitions which were added to Claims 91 and 118. Redacted Claims 91 and 118 assume, as do Claims 91 and 118 in Appendix A, entry of Appellants' Amendment After Final Rejection Pursuant To 37 C.F.R. § 1.116(b).

> of the compound that determines the classification. By changing these values, several patentably distinct and independent compounds are claimed. In order to have unity of invention the compounds must have "a community of chemical or physical characteristics" which justify their inclusion in a common group, and that such inclusion is not repugnant to principles of scientific classification" In re JONES (CCPA) 74 USPQ 149 (see footnote 2). The structural formula IA ... do not have a significant structural feature that is shared by all of its alternatives which is inventive. The structural formula IA ... only ha[s] the -C(O)-NH-CH(R^2)-C(O)-NH- fragment in common. Compounds embraced by formula IA ... are so diverse in nature that a prior art anticipating a claim with respect to one member under 35 USC 102 would not render obvious the same claim under 35 USC 103. This is evidentiary of patentably distinct and independent inventions.
>
> Limiting the claims to compounds wherein W, together with -C(H)$_p$C(=X), and Q form the elected ring system (the benzoazepinone ring) would overcome this rejection. *See Appendix F, Pages 2-3.*

Amendments to Claims 91 and 118 have been requested under 37 C.F.R. § 1.116(b). The requested amendments specify that "W, together with -C(H)pC(=X)- forms ... a fused ... ring." Prior to the requested amendment, said rings were *optionally* fused. *See Claims 91 and 118, Pages 14 and 30 of Appendix A.*

IV. STATUS OF AMENDMENTS

Concurrent with the filing of the instant appeal brief, Appellants have filed an Amendment After Final Rejection canceling Claims 92-95, 104, 109-117, 119-122, 131, and 136-145 and amending Claims 91 and 118. There have been no other amendments filed subsequent to the final rejection.

V. SUMMARY OF THE INVENTION

This invention is directed to compounds which inhibit β-amyloid peptide release and/or synthesis and to compositions comprising those compounds. This invention is useful in the prevention of Alzheimer's Disease ("AD") in patients susceptible to AD and in the treatment of patients currently suffering from AD, as it will prevent further deterioration. *See Appendix C, Page 8, Lines 25-29 of the Specification.*[5]

Brains of individuals with AD exhibit characteristic lesions known as senile plaques, amyloid plaques, amyloid angiopathy (where amyloid deposits in blood vessels), and neurofibrillary tangles. *See Appendix C, Page 6, Lines 24-26 of the Specification.* Patients with AD often have many of these lesions in areas of the brain important for memory and cognitive function. *See Appendix C, Page 6, Lines 26-29 of the Specification.* Amyloid plaques are also characteristic of the brains of individuals with Down's Syndrome (Trisomy 21), and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type ("HCHWA-D"). *See Appendix C, Page 6, Line 31-Page 7, Line 1 of the Specification.*

The primary chemical constituent in the lesions described above is a protein approximately 4.2 kiloDaltons in size, made up of about thirty-nine to forty-three amino acids. *See Appendix C, Page 7, Lines 6-10 of the Specification.* This protein is known as the β-amyloid peptide ("βAP"), Aβ, AβP, or β/A4. *See Appendix C, Page 7, Lines 9-10 of the Specification.* Research has revealed that the β-amyloid peptide is but a small fragment of a larger precursor protein, known as the amyloid precursor protein ("APP"). *See Appendix C, Page 7, Lines 15-17 of the Specification.* The β-amyloid peptide results from enzymatic cleavage of the amyloid precursor protein. *See Appendix C, Page 7, Lines 18-20 of the Specification.*

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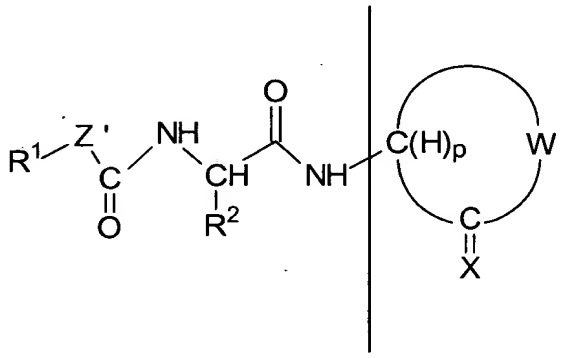
[5] The Specification in this application totals 888 pages. For the convenience of the Board, Appellants have attached, as Appendix C, cited pages of the Specification. Appellants have also attached, as Appendix D, cited pages of the Preliminary Amendment.

The compounds of the claimed invention may be considered N-acetyl substituted amino acid amides and share the following formula:



IA

N-acetyl amino acid amide substituted

See Appendix D, Pages 1-2 of the Preliminary Amendment; see also Appendix C, Page 9, Lines 1-17 of the Specification.

A compound or mixture of compounds of Formula IA may be administered to cells such that the cellular release and/or synthesis of β-amyloid peptide is inhibited. *See Appendix C, Page 12, Lines 21-25 of the Specification.* Such compounds may also be employed in conjunction with a pharmaceutical composition to prophylactically and/or therapeutically prevent and/or treat AD. *See Appendix C, Page 12, Lines 26-Page 13, Line 6 of the Specification.*

Upwards of a thousand compounds according to the invention have been prepared. *See Pages 105-734 of the Specification.*[6] Many of these compounds were tested for their ability to inhibit β-amyloid peptide production in a cell line having a mutation known as "the Swedish mutation." *See Appendix C, Page 735, Lines 1-4 of the Specification; see also Appendix C, Page 7, Line 26-Page 8, Line 14 of the Specification.* It was determined that the tested compounds share the function of inhibiting β-amyloid peptide production by at least 30%, when compared to a control. *See Appendix C, Page 736, Lines 23-26 of the Specification.*

[6] These pages of the Specification are not attached as an Appendix, as such a lengthy attachment may inconvenience the Board.

VI. ISSUE

The sole issue on appeal is whether the Markush group rejection of Claims 91 and 118 is correct.[7]

VII. GROUPING OF CLAIMS

All of the appealed claims will be argued together, and all appealed claims stand or fall together.

VIII. ARGUMENT

As indicated above, the sole issue on appeal is whether the Markush group rejection for the substituted portion of Formula IA in Claims 91 and 118 is correct. Appellants maintain that the Markush groups are proper and that the pending final rejection should be reversed.

A. Requirements of Proper Markush Groups

The term "Markush," as applied to a patent claim, denotes a claim wherein a substance, substituent, agent, reactant, or other material is recited as being from a group consisting of certain specified materials, *e.g.* "a material selected from the group consisting of A, B, C, and D." Manuel C. Rosa, *Outline of Practice Relative to "Markush" Claims*, 34 J.P.O.S. 324 (1952). Markush groups derive their name from *Ex parte Markush*, where Eugene A. Markush eventually claimed his dyes using the language "material selected from the group consisting of aniline, homologues of

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[7] Rejected Claims 91 and 118 possess several variables, including R^1, R^2, Z', W, and p. *See Appendices A and B.* Markush language is used to describe some of these variables. For example, "R^2 is selected from the group consisting of ... ." *See, e.g., Claim 91, Pages 13-14 of Appendix A.* The pending Final Rejections make clear, however, that only the Markush Group for the substituted portion of the molecules has been rejected. The Examiner's Markush rejection reads "[t]he ring formed by W, together with $-C(H)_pC(=X)$, ... are defined in such a way that they keep changing the core of the compound that determines the classification." *See Appendix F, Page 3.* Appellants assume from this language that other Markush groups found in Claims 91 and 118 are not included in the pending Markush rejections. Accordingly, Appellants' appeal brief discusses only the Markush group describing the ring formed by W, together with $-C(H)_pC(=X)$.

aniline and halogen substitutes of aniline." *See Ex parte Markush*, 1925 C.D. 126,127 (Comm'r Pat. 1924).

The propriety of a Markush group is decided on a case-by-case basis. *See In re Harnisch*, 631 F.2d 716, 722 (C.C.P.A. 1980). In deciding the propriety of Markush groups for chemical compounds, one does not look to the Markush group members, but to the compounds as a whole. *See id.* at 722; *see also In re Jones*, 162 F.2d 479, 481 (C.C.P.A. 1947) (stating "[i]n determining the propriety of a Markush grouping, moreover, the compounds which are grouped must each be considered as a whole and should not be broken down into elements or other components"). A proper Markush group for chemical compounds satisfies two criteria: (1) the compounds share a common function, and (2) the compounds are structurally similar. *Harnish*, 631 F.2d at 722. It is reversible error to reject a Markush group satisfying these two criteria. *Harnish*, 631 F.2d at 722-723.

B. Appellants' Markush Groups Are Proper

1. Appellants' Compounds Share A Common Function

Appellants' compounds, as described in Claims 91 and 118, share the common function of inhibiting the synthesis and/or release of the β-amyloid peptide. Appellants' compounds are useful for treating and preventing AD. *See Appendix C, Page 8, Lines 25-29 of the Specification*; *see also Appendix C, Page 736, Lines 23-26 of the Specification*; *see also Appendix A*. Appellants have used a Markush group to define the substituted portion of their compounds because regardless of which alternative is chosen for the substituted portion of a given compound, the compound as a whole will inhibit the synthesis and/or release of the β-amyloid peptide. Appellants' use of a Markush group is proper in this situation because "[i]t is generally understood that in ... describing a class of compounds [using a Markush group] an applicant is, in effect, asserting that the members of the Markush group do not fall within any recognized generic class, but are alternatively usable for the purposes of the invention, and therefore, regardless of which of the alternatives is substituted on the basic structure, the compound as a whole will exhibit the disclosed utility." *In re Driscoll*, 562 F.2d 1245, 1249 (C.C.P.A. 1977). Here, the

substituted portion of Appellants' compounds do not fall within any recognized generic class, but may alternatively be used in conjunction with the N-acetyl amino acid amide portion of Appellants' compounds to inhibit the synthesis and/or release of the β-amyloid peptide.

In both *In re Jones* and *In re Harnisch*, the Court of Customs and Patent Appeals took into account that the claimed compounds shared a common function. Specifically, the Court in *Jones* noted that all of appellant's claimed compounds "are said to be effective agents for stimulating plant growth." *Jones*, 162 F.2d at 480. The Court in *Harnisch* noted similarities to the *Jones* case and concluded that the Board had committed factual error "in not recognizing that all of appellant's claimed compounds are dyes." *Harnisch*, 631 F.2d at 722.

The Board of Patent Appeals and Interferences, in *Ex parte Hozumi*, reversed an examiner's improper Markush rejection in part because the claimed compounds shared the utility of having antimycotic activity. *See Ex parte Hozumi*, 3 U.S.P.Q.2d 1059, 1060 (Bd. Pat. App. & Int. 1984).[8] In *Ex parte Brouard*, the Board reversed a rejection to an allegedly improper Markush group[9] based in part on the fact that all of

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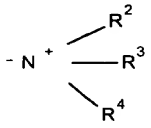
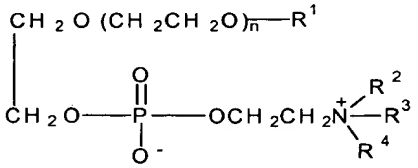
[8] The Markush group under appeal in that case recited a quaternary amine of the formula:



which "represents cyclic ammonio selected from the group consisting of pyridinio, oxazolio, thiazolio, pyridazinio, quinolinio, isoquinolinio, N-C_{1-4} alkylmorpholinio and N-C_{1-4} alkylpiperazinio" and which was included in the formula:

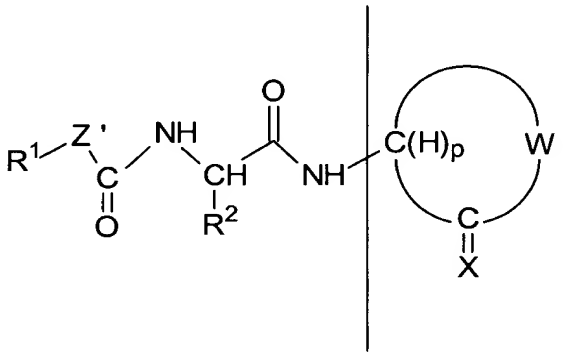


[9] Note the improper Markush rejection in that case was made under 35 U.S.C. § 121, "Claim 24 has been rejected under 35 U.S.C. § 121 on the ground that radical 'B' misjoins independent and distinct inventions and, hence, is drawn to

the claimed compounds were able to dye polyester. *Ex parte Brouard*, 201 U.S.P.Q. 538, 540 (Bd. Pat. App. & Int. 1976). In *Ex parte Taylor*, the Board reversed a rejection for an allegedly improper Markush group and reasoned, "[t]he specification unequivocally states that these compounds with the designated Y substituents are characterized by the ability to form a chelate with certain metal ions and additionally to form photospirans when reacted with a methylene base."[10] *Ex parte Taylor*, 167 U.S.P.Q. 637, 638 (Bd. Pat. App. 1969).

2. Appellants' Compounds Are Structurally Similar

As indicated above, Appellants' compounds may be referred to as N-acetyl substituted amino acid amides, wherein "N-acetyl" refers to the R^1-Z'-C(O)- group; "amino acid amide" refers to the -NH-(CH-R^2)C(O)-NH- group; and "substituted" refers to the cyclic structure in formula IA:



IA

N-acetyl amino acid amide substituted

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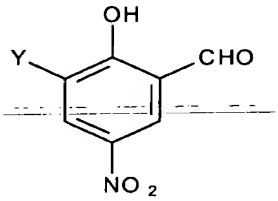
an improper markush group." *Brouard*, 201 U.S.P.Q. at 540.

[10] The Markush group under appeal, "wherein Y is selected from the group consisting of -CH=O, -N=N-R, -CH_2-O-R^1, and -CH_2-N(R^2)-R^3, wherein R is aryl, R^1 is selected from the group consisting of hydrogen, alkyl, and aryl, and each of R^2 and R^3 is selected from the group consisting of alkyl and aryl and R^2 and R^3 taken together may be a divalent aliphatic radical" was included in the formula:



In his rejections, the Examiner wrote "Appellants' compounds "have the -C(O)-NH-CH(R^2)-C(O)-NH- fragment in common." *See Appendix E at Page 3; see also Appendix F at Page 3.* Thus, using Appellants' nomenclature, the Examiner has conceded that the amino acid amide component as well as the -C(O)- portion of the N-acetyl component are common among the compounds. Yet, looking at Appellants' compounds as a whole, each compound has an N-acetyl component, an amino acid amide component, and is substituted. Accordingly, the rejected claims are structurally similar, satisfying the second requirement for a proper Markush group under *Harnisch*.

Compounds alleged to include an improper Markush group must be studied to determine whether they are structurally similar. In *Jones*, the Court of Customs and Patent Appeals reversed the improper Markush group rejection and held that "all the claimed compounds belong to the genus of tetralyl compounds having a substituted methyl group at position 6." *See Jones*, 162 F.2d at 481. In *Harnisch*, the Court reversed the improper Markush group rejection in part because all of the claimed compounds were "all coumarin compounds which the board admitted to be 'a single structural similarity.'"[11] *Harnisch*, 631 F.2d at 722.

The Board of Patent Appeals and Interferences, in *Ex parte Della Bella*, found that the claimed compounds were "all, basically, ... 3-bromo-isoxazol-5-yl derivatives differing amongst each other only in the nature of the 5-substituent. Quite evidently, thus, they all belong to a recognized genus of structurally related materials having a community of physical and chemical properties."[12] *Ex parte Bella Della*, 7

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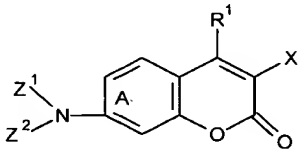
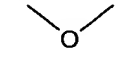
[11] The Markush group under appeal was included in the formula:



[12] The Markush group under appeal, "wherein R is selected from the group consisting of -C(=O)CH_2X, -CH(OH)-CH_2Br, 

U.S.P.Q.2d 1669 (Bd. Pat. App. & Int. 1988). In *Brouard*, the Board noted that all of the claimed compounds contained a cinnamonitrile radical. *Brouard*, 201 U.S.P.Q. at 540.

3. Appellants' Compounds Satisfy the Controlling Two-Part Test

Based on controlling precedent, a proper Markush group for chemical compounds satisfies two criteria: (1) the compounds share a common function, and (2) the compounds are structurally similar. *Harnish*, 631 F.2d at 722. Because Appellants' compounds share the common function of inhibiting β-amyloid peptide synthesis and/or release, the first requirement for a proper chemical Markush group is satisfied. Appellants' compounds are structurally similar because they share the N-acetyl amino acid amide structure and are substituted. Therefore, Appellants' compounds meet the second requirement for a proper chemical Markush group.

Appellants' compounds satisfy the controlling two-part standard for proper chemical Markush groups. The Markush group for the substituted portion of Formula IA in Claims 91 and 118 is not improper.

4. Appellants' Compounds Also Satisfy the M.P.E.P. Standard

The two-part common function and structural similarity test of *In re Harnisch* is the controlling standard for determining the propriety of a chemical Markush group. *See Harnisch*, 631 F.2d at 722. However, the standard recited in Section 803.02 of the M.P.E.P. reads, "it is improper for the [Patent] Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. ... Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility." The M.P.E.P. standard differs from that of *Harnisch* by requiring that the structural

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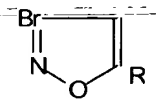
and X is selected from the group consisting of hydrogen and bromine" was included in the formula:



similarity be substantial and essential to the disclosed utility. While Appellants recognize that the M.P.E.P. does not have the force of law and maintain that the *Harnish* standard controls, Appellants submit that their compounds also satisfy the M.P.E.P standard.

As explained above, Appellants' compounds share a common utility. That is, the ability to inhibit the synthesis and/or release of the β-amyloid peptide. Appellants' compounds also share a substantial structural feature — the N-acetyl amino acid amide portion of the compound. The N-acetyl amino acid amide portion of Appellants' compounds must be essential to the compounds' utility because regardless of which substitution is made at the substituted portion of Appellants' compounds, the compounds retain the ability to inhibit the synthesis and/or release of the β-amyloid peptide. *See Appendix C, Page 736, Lines 23-26 of the Specification.*[13] Accordingly, Appellants' compounds satisfy both the *Harnisch* requirements and the standard set forth in the M.P.E.P.

C. ALLEGED JUSTIFICATIONS FOR THE PENDING REJECTIONS ARE CONTRARY TO LAW

The language of the final rejection and the rejection preceding it indicates that the Examiner has rejected Claims 91 and 118 for reasons contrary to law.

1. Rejecting Appellants' Markush Groups Based Solely on an Analysis of the "Core" of Appellants' Compounds Is Error

Claims 91 and 118 were finally rejected "under a judicially created doctrine as being drawn to an improper Markush group, that is, the claims lack unity of invention. The ring formed by W, together with $-C(H)_pC(=X)$, and Q are defined in such a way that they keep changing **the core of the compound** that determines the classification." (bold added) *See Appendix E, Pages 2-3; see also Appendix F, Pages 2-3.*

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[13] Explaining that hundreds of tested compounds, differing in the nature of their substitution, share the function of inhibiting β-amyloid peptide production by at least 30%, when compared to a control.

It is improper to consider the "core" of a compound when determining whether a chemical Markush group is proper. *See Harnisch*, 631 F.2d at 722 (summarizing what was held in *Jones* and stating "in determining the propriety of a Markush grouping the compounds must be considered as wholes and not broken down into elements or other components"). Accordingly, this basis for the rejection of Claims 91 and 118 is contrary to law.

2. Rejecting Appellants' Markush Groups Based on the Compounds' Classification Is Error

Claims 91 and 118 also were finally rejected in part because "[t]he ring formed by W, together with -$C(H)_pC(=X)$ ... are defined in such a way that they keep changing the core of the compound **that determines the classification**." (bold added) *See Appendix E, Page 2; see also Appendix F, Pages 2-3.* Neither the classification of Markush Group members nor the effort required to search such classes is relevant to the propriety of a Markush Group. In *Ex parte Brouard*, the Board stated:

> [t]he fact that the various groups of compounds corresponding to [the rejected claim] are classified in different subclasses does not mean that it would be repugnant to accepted principles of scientific classification to associate them together as a genus; on the contrary the fact that all of the claimed compounds share a common ... group and have the capability to dye polyester fibers suggests that it would not be repugnant to scientific classification to associate them together as a genus. ... the fact that different fields of search are involved does not establish that the Markush group is improper.

Brouard, 201 U.S.P.Q. at 540; *see also Taylor*, 167 U.S.P.Q. at 637 (stating that the extent of an examiner's search does not provide support for an improper Markush rejection). Accordingly, the Examiner's rejection based on the classification of the core of Appellants' compounds is improper.

IX. REQUEST FOR ORAL HEARING

Appellants request an oral hearing. Concurrent with the filing of this Brief, Appellants are filing, in duplicate, a Request for Oral Hearing in this case.

X. CONCLUSION

Appellants' Markush Groups are proper. Appellants' compounds are N-acetyl substituted amino acid amides which are useful for inhibiting β-amyloid peptide synthesis and/or release. Considering Appellants' compounds as a whole and on the facts of this case, it is apparent that these compounds possess a common function and are structurally similar. The Examiner's alleged justifications for rejecting Claims 91 and 118 are contrary to law. Appellants' maintain that the Markush group for the substituted portion of Formula IA in Claims 91 and 118 is proper. Appellants respectfully request reversal of the outstanding improper Markush rejections.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By:_____
Bruce T. Wieder
Registration No. 33,815

With Mr. Wieder on the Brief are:
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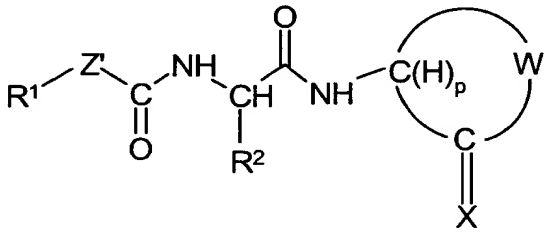
APPENDIX A

Claims 91 and 118 from U.S. Application 09/916,440

91. A pharmaceutical composition comprising a pharmaceutically inert carrier and a pharmaceutically effective amount of formula IA:



IA

wherein R^1 is selected from the group consisting of:

A) alkyl of from 1 to 10 carbon atoms;

B) alkenyl of from 2 to 10 carbon atoms and 1-2 sites of alkenyl unsaturation;

C) alkynyl of from 2 to 10 carbon atoms and from 1-2 sites of alkynyl unsaturation;

D) cycloalkyl of from 3 to 12 carbon atoms;

E) cycloalkenyl of from 4 to 8 carbon atoms;

F) substituted alkyl of from 1 to 10 carbon atoms, having from 1 to 3 substituents selected from:

1) alkoxy of from 1 to 10 carbon atoms;

2) substituted alkoxy of the formula substituted alkyl-O- where substituted alkyl is as defined in F herein;

3) cycloalkyl which is as defined in D herein;

4) substituted cycloalkyl is defined in I herein;

5) cycloalkenyl which is defined in E herein;

6) substituted cycloalkenyl which is defined in J herein;

7) acyl selected from alkyl-C(O)-, substituted alkyl-C(O)-,

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cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein cycloalkyl is defined in D herein; wherein substituted cycloalkyl is defined in I herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

8) acylamino having the formula -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

9) acyloxy selected from alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein cycloalkyl is defined in D herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

10) amino;

11) aminoacyl having the formula -NRC(O)R wherein each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic; wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

12) aminoacyloxy having the formula -NRC(O)OR wherein each R is independently selected from the group consisting of hydrogen,

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alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic; wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

13) cyano;

14) halogen;

15) hydroxyl;

16) carboxyl;

17) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;

18) thiol;

19) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;

20) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;

21) aryl having from 6 to 14 ring carbon atoms, optionally substituted with from 1 to 5 substituents selected from the group consisting of:

a) hydroxy;

b) acyl as defined in F7 herein;

c) acyloxy as defined in F9 herein;

d) alkyl as defined in A herein;

e) substituted alkyl as defined in F herein;

f) alkoxy as defined in F1 herein;

g) substituted alkoxy as defined in F2 herein;

h) alkenyl as defined in B herein;

i) substituted alkenyl as defined in G herein;

j) alkynyl as defined in C herein;

k) substituted alkynyl as defined in H herein;

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l) amino;

m) aminoacyl as defined in F11 herein;

n) acylamino as defined in F8 herein;

o) alkaryl of the formula -alkylene-aryl having 8 carbon atoms in the alkylene moiety and aryl is defined in F21 herein;

p) aryl as defined in F21 herein;

q) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;

r) azido;

s) carboxyl;

t) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;

u) cyano;

v) halo selected from fluoro, chloro, bromo and iodo;

w) nitro;

x) heteroaryl as defined in F22 herein;

y) heterocyclic as defined in F23 herein;

z) aminoacyloxy as defined in F12 herein;

aa) oxyacylamino having the formula -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

bb) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;

cc) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;

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dd) thioaryloxy having the formula -S-aryl wherein aryl is defined in F21 herein;

ee) thioheteroaryloxy having the formula -S-heteroaryl wherein heteroaryl is defined F22 herein;

ff) -SO-alkyl wherein alkyl is defined in A herein;

gg) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;

hh) -SO-aryl wherein aryl is defined in F21 herein;

ii) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

jj) $-SO_2$-alkyl wherein alkyl is defined in A herein;

kk) $-SO_2$-substituted alkyl wherein substituted alkyl is defined in F herein;

ll) $-SO_2$-aryl wherein aryl is defined in F21 herein;

mm) $-SO_2$-heteroaryl wherein heteroaryl is defined in F22 herein;

nn) trihalomethyl wherein halo is defined in I20 herein;

oo) mono- and dialkylamino wherein alkyl is defined in A herein;

pp) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

qq) mono- and di-arylamino wherein aryl is defined in F21 herein;

rr) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

ss) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein;

tt) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A

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herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

22) heteroaryl of from 1 to 15 ring carbon atoms and 1 to 4 ring heteroatoms selected from oxygen, nitrogen and sulfur, optionally substituted with from 1 to 5 substituents selected from:

a) alkyl as defined in A herein;
b) substituted alkyl as defined in F herein;
c) alkoxy as defined in F1 herein;
d) substituted alkoxy as defined in F2 herein;
e) aryl as defined in F21 herein;
f) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;
g) halo selected from fluoro, chloro, bromo and iodo;
h) nitro;
i) heteroaryl as defined in F22 herein;
j) thiol;
k) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;
l) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;
m) thioaryloxy having the formula -S-aryl wherein aryl is defined in F21 herein; and
n) trihalomethyl wherein halo is defined in I20 herein;

23) heterocyclic of from 1 to 15 ring carbon atoms and from 1 to 4 ring atoms selected from nitrogen, sulfur and oxygen, optionally substituted with from 1 to 5 substituents selected from:

a) alkyl as defined in A herein;

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b) substituted alkyl as defined in F herein;

c) alkoxy as defined in F1 herein;

d) substituted alkoxy as defined in F2 herein;

e) aryl as defined in F21 herein;

f) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;

g) halo selected from fluoro, chloro, bromo and iodo;

h) nitro;

i) heteroaryl as defined in F22 herein;

j) thiol;

k) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;

l) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;

m) thioaryloxy having the formula -S-aryl wherein aryl is defined in F21 herein; and

n) trihalomethyl wherein halo is selected from fluoro, chloro, bromo and iodo;

24) aryloxy of the formula -O-aryl wherein aryl is defined in F21 herein;

25) heteroaryloxy of the formula -O-heteroaryl wherein heteroaryl is defined in F22 herein;

26) hydroxyamino;

27) alkoxyamino wherein alkoxy is defined in F1 herein;

28) nitro;

29) -SO-alkyl wherein alkyl is defined in A herein;

30) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;

31) -SO-aryl wherein aryl is defined in F21 herein;

32) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

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33) $-SO_2$-alkyl wherein alkyl is defined in A herein;

34) $-SO_2$-substituted alkyl wherein substituted alkyl is defined in F herein;

35) $-SO_2$-aryl wherein aryl is defined in F21 herein;

36) $-SO_2$-heteroaryl wherein heteroaryl is defined in F22 herein;

37) mono- and dialkylamino wherein alkyl is defined in A herein;

38) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

39) mono- and di-arylamino wherein aryl is defined in F21 herein;

40) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

41) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein;

42) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

G) substituted alkenyl having from 1 to 3 substituents selected from the group consisting of:

1) alkoxy as defined in F1 herein;

2) substituted alkoxy as defined in F2 herein;

3) acyl as defined in F7 herein;

4) acylamino as defined in F8 herein;

5) acyloxy as defined in F9 herein;

6) amino;

7) aminoacyl as defined in F11 herein;

8) aminoacyloxy as defined in F12 herein;

9) cyano;

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10) halogen selected from fluoro, chloro, bromo and iodo;
11) hydroxyl;
12) carboxyl;
13) carboxylalkyl as defined in F17 herein;
14) thiol;
15) thioalkoxy as defined in F19 herein;
16) substituted thioalkoxy as defined in F20 herein;
17) aryl as defined in F21 herein;
18) heteroaryl as defined in F22 herein;
19) heterocyclic as defined in F23 herein;
20) nitro;
21) -SO-alkyl wherein alkyl is defined in A herein;
22) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;
23) -SO-aryl wherein aryl is defined in F21 herein;
24) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;
25) $-SO_2$-alkyl wherein alkyl is defined in A herein;
26) $-SO_2$-substituted alkyl wherein substituted alkyl is defined in F herein;
27) $-SO_2$-aryl wherein aryl is defined in F21 herein;
28) $-SO_2$-heteroaryl wherein heteroaryl is defined in F22 herein;
29) mono- and dialkylamino wherein alkyl is defined in A herein;
30) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;
31) mono- and di-arylamino wherein aryl is defined in F21 herein;
32) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;
33) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein; and

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34) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

H) substituted alkynyl of from 1 to 3 substituents selected from:

1) alkoxy as defined in F1 herein;
2) substituted alkoxy as defined in F2 herein;
3) acyl as defined in F7 herein;
4) acylamino as defined in F8 herein;
5) acyloxy as defined in F9 herein;
6) amino;
7) aminoacyl as defined in F11 herein;
8) aminoacyloxy as defined in F12 herein;
9) cyano;
10) halogen selected from fluoro, chloro, bromo and iodo;
11) hydroxyl;
12) carboxyl;
13) carboxylalkyl as defined in F17 herein;
14) thiol;
15) thioalkoxy as defined in F19 herein;
16) substituted thioalkoxy as defined in F20 herein;
17) aryl as defined in F21 herein;
18) heteroaryl as defined in F22 herein;
19) heterocyclic as defined in F23 herein;
20) nitro;
21) -SO-alkyl wherein alkyl is defined in A herein;
22) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;

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23) -SO-aryl wherein aryl is defined in F21 herein;

24) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

25) -SO_2-alkyl wherein alkyl is defined in A herein;

26) -SO_2-substituted alkyl wherein substituted alkyl is defined in F herein;

27) -SO_2-aryl wherein aryl is defined in F21 herein;

28) -SO_2-heteroaryl wherein heteroaryl is defined in F22 herein;

29) mono- and dialkylamino wherein alkyl is defined in A herein;

30) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

31) mono- and di-arylamino wherein aryl is defined in F21 herein;

32) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

33) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein; and

34) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

l) substituted cycloalkyl having 3 to 12 carbon atoms and from 1 to 5 substituents selected from the group consisting of:

1) hydroxy;

2) acyl as defined in F7 herein;

3) acyloxy as defined in F9 herein;

4) alkyl as defined in A herein;

5) substituted alkyl as defined in F herein;

6) alkoxy as defined in F1 herein;

7) substituted alkoxy as defined in F2 herein;

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8) alkenyl as defined in B herein;
9) substituted alkenyl as defined in G herein;
10) alkynyl as defined in C herein;
11) substituted alkynyl as defined in H herein;
12) amino;
13) aminoacyl as defined in F11 herein;
14) alkaryl of the formula -alkylene-aryl having 8 carbon atoms in the alkylene moiety and aryl is defined in F21 herein;
15) aryl as defined in F21 herein;
16) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;
17) carboxyl;
18) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;
19) cyano;
20) halo selected from fluoro, chloro, bromo and iodo;
21) nitro;
22) heteroaryl as defined in F22 herein;
23) thioalkoxy as defined in F19 herein;
24) substituted thioalkoxy as defined in F20 herein; and
25) trihalomethyl wherein halo is selected from fluoro, chloro, bromo and iodo;

J) substituted cycloalkenyl having from 4 to 8 carbon atoms and from 1 to 5 substituents selected from the group consisting of:

1) hydroxy;
2) acyl as defined in F7 herein;
3) acyloxy as defined in F9 herein;
4) alkyl as defined in A herein;
5) substituted alkyl as defined in F herein;
6) alkoxy as defined in F1 herein;

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7) substituted alkoxy as defined in F2 herein;
8) alkenyl as defined in B herein;
9) substituted alkenyl as defined in G herein;
10) alkynyl as defined in C herein;
11) substituted alkynyl as defined in H herein;
12) amino;
13) aminoacyl as defined in F11 herein;
14) alkaryl of the formula -alkylene-aryl having 8 carbon atoms in the alkylene moiety and aryl is defined in F21 herein;
15) aryl as defined in F21 herein;
16) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;
17) carboxyl;
18) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;
19) cyano;
20) halo selected from fluoro, chloro, bromo and iodo;
21) nitro;
22) heteroaryl as defined in F22 herein;
23) thioalkoxy as defined in F19 herein;
24) substituted thioalkoxy as defined in F20 herein; and
25) trihalomethyl wherein halo is selected from fluoro, chloro, bromo and iodo;

K) aryl as defined in F21 herein;
L) heteroaryl as defined in F22 herein; and
M) heterocyclic as defined in F23 herein;

R^2 is independently selected from the group consisting of:

N) alkyl as defined in A herein;
O) alkenyl as defined in B herein;

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P) alkynyl as defined in C herein;

Q) substituted alkyl as defined in F herein;

R) substituted alkenyl as defined in G herein;

S) substituted alkynyl as defined in H herein;

T) cycloalkyl as defined in D herein;

U) aryl as defined in F21 herein;

V) heteroaryl as defined in F22 herein;

W) heterocyclic as defined in F23 herein;

W^{1}) 2-aminopyrid-6-yl;

W^{2}) 2-methylcyclopentyl;

W^{3}) cyclohex-2-enyl; and

W^{4}) $-(CH_2)_4NHC(O)OC(CH_3)_3$;

Z' is represented by the formula -CX'X"-, $-T-CH_2-$ or -T-C(O)-, where T is selected from the group consisting of oxygen, sulfur, $-NR^5$, where R^5 is hydrogen, acyl as defined in F7 herein, alkyl as defined in A herein, aryl as defined in F21 herein, or heteroaryl as defined in F22 herein; X′ is hydrogen, hydroxy or fluoro; X″ is hydrogen, hydroxy or fluoro, or X′ and X″ together form an oxo group;

W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl as defined in D herein, cycloalkenyl as defined in E herein, heterocyclic as defined in F23 herein, cycloalkyl as defined in I herein, substituted cycloalkenyl as defined in J herein, wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of cycloalkyl as defined in D herein, cycloalkenyl as defined in E herein, heterocyclic as defined in F23 herein, aryl as defined in F21 herein, and heteroaryl as defined in F22 herein, where, in turn, each of said ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy as defined in F1 herein, substituted alkoxy as defined in F2 herein, thioalkoxy as defined in F19 herein, substituted thioalkoxy as defined in F20 herein, nitro, cyano, carboxyl, carboxyl

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esters, alkyl as defined in A herein, substituted alkyl as defined in F herein, alkenyl as defined in B herein, substituted alkenyl as defined in G herein, alkynyl as defined in C herein, substituted alkynyl as defined in H herein, amino, N-alkylamino wherein alkyl is defined in A herein, N,N-dialkylamino wherein alkyl is defined in A herein, N-substituted alkylamino wherein substituted alkyl is defined in F herein, N-alkyl N-substituted alkylamino wherein alkyl is defined in A herein and wherein substituted alkyl is defined in F herein, N-N-disubstituted alkylamino wherein substituted alkyl is defined in F herein, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$, and $-S(O)_2NR^4R^4$, where each R^4 is independently selected from the group consisting of alkyl as defined in A herein, substituted alkyl as defined in F herein, or substituted aryl as defined in F21 herein;

X is selected from the group consisting of =O; =S; -H, -OH; H,-SH; and H,H;

p is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by W and $-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to NH, and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

or pharmaceutically acceptable salts thereof;

with the following provisos:

AAA. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;

BBB. when R^1 is phenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, *p* is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;

CCC. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;

DDD. when R^1 is 4-chlorobenzoyl-CH_2-, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

EEE. when R^1 is 2-phenylphenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

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FFF. when R^1 is $CH_3OC(O)CH_2$-, R^2 is -CH_3, Z′ is -CH_2-, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

GGG. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $CH_3OC(O)CH_2$-, 4-$HOCH_2$-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S-, R^2 is -CH_3, Z′ is -CH_2-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

HHH. when R^1 is 2,6-difluorophenyl, R^2 is -CH_3, Z′ is -CH(OH)-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

III. when the ring defined by W and -$C(H)_pC(=X)$- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

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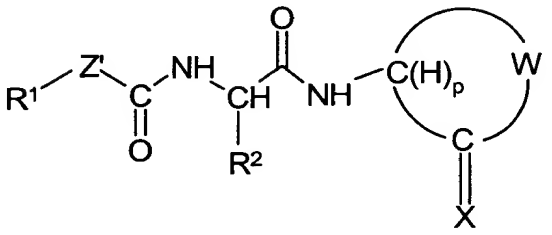
118. (Amended) A compound of formula IA:



IA

wherein R^1 is selected from the group consisting of:

A) alkyl of from 1 to 10 carbon atoms;

B) alkenyl of from 2 to 10 carbon atoms and 1-2 sites of alkenyl unsaturation;

C) alkynyl of from 2 to 10 carbon atoms and from 1-2 sites of alkynyl unsaturation;

D) cycloalkyl of from 3 to 12 carbon atoms;

E) cycloalkenyl of from 4 to 8 carbon atoms;

F) substituted alkyl of from 1 to 10 carbon atoms, having from 1 to 3 substituents selected from:

1) alkoxy of from 1 to 10 carbon atoms;

2) substituted alkoxy of the formula substituted alkyl-O- where substituted alkyl is as defined in F herein;

3) cycloalkyl which is as defined in D herein;

4) substituted cycloalkyl is defined in I herein;

5) cycloalkenyl which is defined in E herein;

6) substituted cycloalkenyl which is defined in J herein;

7) acyl selected from alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein cycloalkyl is defined in D herein; wherein substituted

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cycloalkyl is defined in I herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

8) acylamino having the formula -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

9) acyloxy selected from alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein cycloalkyl is defined in D herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

10) amino;

11) aminoacyl having the formula -NRC(O)R wherein each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic; wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

12) aminoacyloxy having the formula -NRC(O)OR wherein each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic; wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein;

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wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

13) cyano;

14) halogen;

15) hydroxyl;

16) carboxyl;

17) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;

18) thiol;

19) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;

20) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;

21) aryl having from 6 to 14 ring carbon atoms, optionally substituted with from 1 to 5 substituents selected from the group consisting of:

a) hydroxy;

b) acyl as defined in F7 herein;

c) acyloxy as defined in F9 herein;

d) alkyl as defined in A herein;

e) substituted alkyl as defined in F herein;

f) alkoxy as defined in F1 herein;

g) substituted alkoxy as defined in F2 herein;

h) alkenyl as defined in B herein;

i) substituted alkenyl as defined in G herein;

j) alkynyl as defined in C herein;

k) substituted alkynyl as defined in H herein;

l) amino;

m) aminoacyl as defined in F11 herein;

n) acylamino as defined in F8 herein;

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o) alkaryl of the formula -alkylene-aryl having 8 carbon atoms in the alkylene moiety and aryl is defined in F21 herein;

p) aryl as defined in F21 herein;

q) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;

r) azido;

s) carboxyl;

t) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;

u) cyano;

v) halo selected from fluoro, chloro, bromo and iodo;

w) nitro;

x) heteroaryl as defined in F22 herein;

y) heterocyclic as defined in F23 herein;

z) aminoacyloxy as defined in F12 herein;

aa) oxyacylamino having the formula -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

bb) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;

cc) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;

dd) thioaryloxy having the formula -S-aryl wherein aryl is defined in F21 herein;

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ee) thioheteroaryloxy having the formula -S-heteroaryl wherein heteroaryl is defined F22 herein;

ff) -SO-alkyl wherein alkyl is defined in A herein;

gg) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;

hh) -SO-aryl wherein aryl is defined in F21 herein;

ii) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

jj) $-SO_2$-alkyl wherein alkyl is defined in A herein;

kk) $-SO_2$-substituted alkyl wherein substituted alkyl is defined in F herein;

ll) $-SO_2$-aryl wherein aryl is defined in F21 herein;

mm) $-SO_2$-heteroaryl wherein heteroaryl is defined in F22 herein;

nn) trihalomethyl wherein halo is defined in I20 herein;

oo) mono- and dialkylamino wherein alkyl is defined in A herein;

pp) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

qq) mono- and di-arylamino wherein aryl is defined in F21 herein;

rr) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

ss) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein;

tt) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl

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is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

22) heteroaryl of from 1 to 15 ring carbon atoms and 1 to 4 ring heteroatoms selected from oxygen, nitrogen and sulfur, optionally substituted with from 1 to 5 substituents selected from:

a) alkyl as defined in A herein;
b) substituted alkyl as defined in F herein;
c) alkoxy as defined in F1 herein;
d) substituted alkoxy as defined in F2 herein;
e) aryl as defined in F21 herein;
f) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;
g) halo selected from fluoro, chloro, bromo and iodo;
h) nitro;
i) heteroaryl as defined in F22 herein;
j) thiol;
k) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;
l) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;
m) thioaryloxy having the formula -S-aryl wherein aryl is defined in F21 herein; and
n) trihalomethyl wherein halo is defined in I20 herein;

23) heterocyclic of from 1 to 15 ring carbon atoms and from 1 to 4 ring atoms selected from nitrogen, sulfur and oxygen, optionally substituted with from 1 to 5 substituents selected from:

a) alkyl as defined in A herein;
b) substituted alkyl as defined in F herein;
c) alkoxy as defined in F1 herein;

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d) substituted alkoxy as defined in F2 herein;

e) aryl as defined in F21 herein;

f) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;

g) halo selected from fluoro, chloro, bromo and iodo;

h) nitro;

i) heteroaryl as defined in F22 herein;

j) thiol;

k) thioalkoxy having the formula -S-alkyl, wherein alkyl is defined in A herein;

l) substituted thioalkoxy having the formula -S-substituted alkyl, wherein substituted alkyl is defined in F herein;

m) thioaryloxy having the formula -S-aryl wherein aryl is defined in F21 herein; and

n) trihalomethyl wherein halo is selected from fluoro, chloro, bromo and iodo;

24) aryloxy of the formula -O-aryl wherein aryl is defined in F21 herein;

25) heteroaryloxy of the formula -O-heteroaryl wherein heteroaryl is defined in F22 herein;

26) hydroxyamino;

27) alkoxyamino wherein alkoxy is defined in F1 herein;

28) nitro;

29) -SO-alkyl wherein alkyl is defined in A herein;

30) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;

31) -SO-aryl wherein aryl is defined in F21 herein;

32) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

33) $-SO_2$-alkyl wherein alkyl is defined in A herein;

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34) -SO_2-substituted alkyl wherein substituted alkyl is defined in F herein;

35) -SO_2-aryl wherein aryl is defined in F21 herein;

36) -SO_2-heteroaryl wherein heteroaryl is defined in F22 herein;

37) mono- and dialkylamino wherein alkyl is defined in A herein;

38) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

39) mono- and di-arylamino wherein aryl is defined in F21 herein;

40) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

41) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein;

42) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

G) substituted alkenyl having from 1 to 3 substituents selected from the group consisting of:

1) alkoxy as defined in F1 herein;

2) substituted alkoxy as defined in F2 herein;

3) acyl as defined in F7 herein;

4) acylamino as defined in F8 herein;

5) acyloxy as defined in F9 herein;

6) amino;

7) aminoacyl as defined in F11 herein;

8) aminoacyloxy as defined in F12 herein;

9) cyano;

10) halogen selected from fluoro, chloro, bromo and iodo;

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11) hydroxyl;

12) carboxyl;

13) carboxylalkyl as defined in F17 herein;

14) thiol;

15) thioalkoxy as defined in F19 herein;

16) substituted thioalkoxy as defined in F20 herein;

17) aryl as defined in F21 herein;

18) heteroaryl as defined in F22 herein;

19) heterocyclic as defined in F23 herein;

20) nitro;

21) -SO-alkyl wherein alkyl is defined in A herein;

22) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;

23) -SO-aryl wherein aryl is defined in F21 herein;

24) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

25) $-SO_2$-alkyl wherein alkyl is defined in A herein;

26) $-SO_2$-substituted alkyl wherein substituted alkyl is defined in F herein;

27) $-SO_2$-aryl wherein aryl is defined in F21 herein;

28) $-SO_2$-heteroaryl wherein heteroaryl is defined in F22 herein;

29) mono- and dialkylamino wherein alkyl is defined in A herein;

30) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

31) mono- and di-arylamino wherein aryl is defined in F21 herein;

32) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

33) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein; and

34) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and

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heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

H) substituted alkynyl of from 1 to 3 substituents selected from:

1) alkoxy as defined in F1 herein;
2) substituted alkoxy as defined in F2 herein;
3) acyl as defined in F7 herein;
4) acylamino as defined in F8 herein;
5) acyloxy as defined in F9 herein;
6) amino;
7) aminoacyl as defined in F11 herein;
8) aminoacyloxy as defined in F12 herein;
9) cyano;
10) halogen selected from fluoro, chloro, bromo and iodo;
11) hydroxyl;
12) carboxyl;
13) carboxylalkyl as defined in F17 herein;
14) thiol;
15) thioalkoxy as defined in F19 herein;
16) substituted thioalkoxy as defined in F20 herein;
17) aryl as defined in F21 herein;
18) heteroaryl as defined in F22 herein;
19) heterocyclic as defined in F23 herein;
20) nitro;
21) -SO-alkyl wherein alkyl is defined in A herein;
22) -SO-substituted alkyl wherein substituted alkyl is defined in F herein;
23) -SO-aryl wherein aryl is defined in F21 herein;
24) -SO-heteroaryl wherein heteroaryl is defined in F22 herein;

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25) $-SO_2$-alkyl wherein alkyl is defined in A herein;

26) $-SO_2$-substituted alkyl wherein substituted alkyl is defined in F herein;

27) $-SO_2$-aryl wherein aryl is defined in F21 herein;

28) $-SO_2$-heteroaryl wherein heteroaryl is defined in F22 herein;

29) mono- and dialkylamino wherein alkyl is defined in A herein;

30) mono- and di-substituted alkylamino wherein substituted alkyl is defined in F herein;

31) mono- and di-arylamino wherein aryl is defined in F21 herein;

32) mono- and di-heteroarylamino wherein heteroaryl is defined in F22 herein;

33) mono- and di-heterocyclicamino wherein heterocyclic is defined in F23 herein; and

34) unsymmetric di-substituted amino having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic wherein alkyl is defined in A herein; wherein substituted alkyl is defined in F herein; wherein aryl is defined in F21 herein; wherein heteroaryl is defined in F22 herein; and wherein heterocyclic is defined in F23 herein;

l) substituted cycloalkyl having 3 to 12 carbon atoms and from 1 to 5 substituents selected from the group consisting of:

1) hydroxy;

2) acyl as defined in F7 herein;

3) acyloxy as defined in F9 herein;

4) alkyl as defined in A herein;

5) substituted alkyl as defined in F herein;

6) alkoxy as defined in F1 herein;

7) substituted alkoxy as defined in F2 herein;

8) alkenyl as defined in B herein;

9) substituted alkenyl as defined in G herein;

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10) alkynyl as defined in C herein;
11) substituted alkynyl as defined in H herein;
12) amino;
13) aminoacyl as defined in F11 herein;
14) alkaryl of the formula -alkylene-aryl having 8 carbon atoms in the alkylene moiety and aryl is defined in F21 herein;
15) aryl as defined in F21 herein;
16) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;
17) carboxyl;
18) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;
19) cyano;
20) halo selected from fluoro, chloro, bromo and iodo;
21) nitro;
22) heteroaryl as defined in F22 herein;
23) thioalkoxy as defined in F19 herein;
24) substituted thioalkoxy as defined in F20 herein; and
25) trihalomethyl wherein halo is selected from fluoro, chloro, bromo and iodo;

J) substituted cycloalkenyl having from 4 to 8 carbon atoms and from 1 to 5 substituents selected from the group consisting of:

1) hydroxy;
2) acyl as defined in F7 herein;
3) acyloxy as defined in F9 herein;
4) alkyl as defined in A herein;
5) substituted alkyl as defined in F herein;
6) alkoxy as defined in F1 herein;
7) substituted alkoxy as defined in F2 herein;
8) alkenyl as defined in B herein;

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9) substituted alkenyl as defined in G herein;
10) alkynyl as defined in C herein;
11) substituted alkynyl as defined in H herein;
12) amino;
13) aminoacyl as defined in F11 herein;
14) alkaryl of the formula -alkylene-aryl having 8 carbon atoms in the alkylene moiety and aryl is defined in F21 herein;
15) aryl as defined in F21 herein;
16) aryloxy having the formula -O-aryl wherein aryl is defined in F21 herein;
17) carboxyl;
18) carboxylalkyl having the formula "-C(O)Oalkyl" wherein alkyl is defined in A herein;
19) cyano;
20) halo selected from fluoro, chloro, bromo and iodo;
21) nitro;
22) heteroaryl as defined in F22 herein;
23) thioalkoxy as defined in F19 herein;
24) substituted thioalkoxy as defined in F20 herein; and
25) trihalomethyl wherein halo is selected from fluoro, chloro, bromo and iodo;

K) aryl as defined in F21 herein;
L) heteroaryl as defined in F22 herein; and
M) heterocyclic as defined in F23 herein;

R^2 is independently selected from the group consisting of:

N) alkyl as defined in A herein;
O) alkenyl as defined in B herein;
P) alkynyl as defined in C herein;
Q) substituted alkyl as defined in F herein;

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R) substituted alkenyl as defined in G herein;

S) substituted alkynyl as defined in H herein;

T) cycloalkyl as defined in D herein;

U) aryl as defined in F21 herein;

V) heteroaryl as defined in F22 herein;

W) heterocyclic as defined in F23 herein;

W^{1}) 2-aminopyrid-6-yl;

W^{2}) 2-methylcyclopentyl;

W^{3}) cyclohex-2-enyl; and

W^{4}) $-(CH_2)_4NHC(O)OC(CH_3)_3$;

Z′ is represented by the formula -CX′X″-, -T-CH_2- or -T-C(O)-, where T is selected from the group consisting oxygen, sulfur, $-NR^5$ where R^5 is hydrogen, acyl as defined in F7 herein, alkyl as defined in A herein, aryl as defined in F21 herein, or heteroaryl as defined in F22 herein;

W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl as defined in D herein, cycloalkenyl as defined in E herein, heterocyclic as defined in F23 herein, cycloalkyl as defined in I herein, substituted cycloalkenyl as defined in J herein, wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of cycloalkyl as defined in D herein, cycloalkenyl as defined in E herein, heterocyclic as defined in F23 herein, aryl as defined in F21 herein, and heteroaryl as defined in F22 herein, where, in turn, each of said ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy as defined in F1 herein, substituted alkoxy as defined in F2 herein, thioalkoxy as defined in F19 herein, substituted thioalkoxy as defined in F20 herein, nitro, cyano, carboxyl, carboxyl esters, alkyl as defined in A herein, substituted alkyl as defined in F herein, alkenyl as defined in B herein, substituted alkenyl as defined in G herein, alkynyl as defined

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in C herein, substituted alkynyl as defined in H herein, amino, N-alkylamino wherein alkyl is defined in A herein, N,N-dialkylamino wherein alkyl is defined in A herein, N-substituted alkylamino wherein substituted alkyl is defined in F herein, N-alkyl N-substituted alkylamino wherein alkyl is defined in A herein and wherein substituted alkyl is defined in F herein, N-N-disubstituted alkylamino wherein substituted alkyl is defined in F herein, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$, and $-S(O)_2NR^4R^4$, where each R^4 is independently selected from the group consisting of alkyl as defined in A herein, substituted alkyl as defined in F herein, or substituted aryl as defined in F21 herein;

X is selected from the group consisting of =O; =S; -H, -OH; H,-SH; and H,H;

p is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by W and $-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to NH, and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

or pharmaceutically acceptable salts thereof;

with the following provisos:

AAA. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;

BBB. when R^1 is phenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, *p* is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;

CCC. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;

DDD. when R^1 is 4-chlorobenzoyl-CH_2-, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

EEE. when R^1 is 2-phenylphenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

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FFF. when R^1 is $CH_3OC(O)CH_2$-, R^2 is -CH_3, Z′ is -CH_2-, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

GGG. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $CH_3OC(O)CH_2$-, 4-$HOCH_2$-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S-, R^2 is -CH_3, Z′ is -CH_2-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

HHH. when R^1 is 2,6-difluorophenyl, R^2 is -CH_3, Z′ is -CH(OH)-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

III. when the ring defined by W and -$C(H)_pC(=X)$- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

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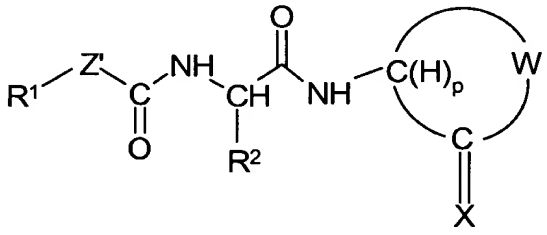
91. A pharmaceutical composition comprising a pharmaceutically inert carrier and a pharmaceutically effective amount of formula IA:



IA

wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

Z′ is represented by the formula -CX′X″-, -T-CH_2- or -T-C(O)- where T is selected from the group consisting oxygen, sulfur, -NR^5 where R^5 is hydrogen, acyl, alkyl, optionally substituted aryl or optionally substituted heteroaryl group; X′ is hydrogen, hydroxy or fluoro; X″ is hydrogen, hydroxy or fluoro, or X′ and X″ together form an oxo group;

R^2 is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, 2-aminopryrid-6-yl,
2-methylcyclopentyl, cyclohex-2-enyl and -$(CH_2)_4NHC(O)OC(CH_3)_3$;

W, together with -$C(H)_pC(=X)$-, forms a cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy,

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thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino,
N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$,
$-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or optionally substituted aryl;

X is selected from the group consisting of =O; =S; -H, -OH; H,-SH; and H,H;

p is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by W and
$-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to NH and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

and pharmaceutically acceptable salts thereof;

with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;

B. when R^1 is phenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, *p* is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;

C. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;

D. when R^1 is 4-chlorobenzoyl-CH_2-, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

E. when R^1 is 2-phenylphenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

F. when R^1 is $CH_3OC(O)CH_2-$, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

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G. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $CH_3OC(O)CH_2$-, 4-$HOCH_2$-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S-, R^2 is -CH_3, Z′ is -CH_2-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

H. when R^1 is 2,6-difluorophenyl, R^2 is -CH_3, Z′ is -CH(OH)-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when the ring defined by W and -$C(H)_pC(=X)$- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

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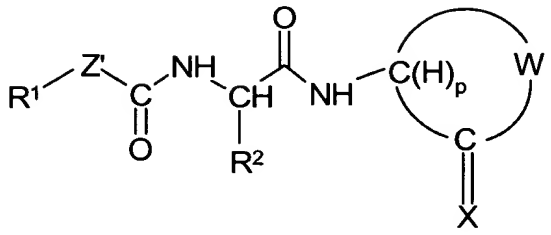
118. A compound of formula IA:



IA

wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

Z′ is represented by the formula -CX′X″-, -T-CH_2- or -T-C(O)- where T is selected from the group consisting oxygen, sulfur, -NR^5 where R^5 is hydrogen, acyl, alkyl, optionally substituted aryl or optionally substituted heteroaryl group; X′ is hydrogen, hydroxy or fluoro; X″ is hydrogen, hydroxy or fluoro, or X′ and X″ together form an oxo group;

R^2 is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, 2-aminopryrid-6-yl,
2-methylcyclopentyl, cyclohex-2-enyl and -$(CH_2)_4NHC(O)OC(CH_3)_3$;

W, together with -$C(H)_pC(=X)$-, forms a cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl,

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substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino,
N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$,
$-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or optionally substituted aryl;

X is selected from the group consisting of =O; =S; -H, -OH; H,-SH; and H,H;

p is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by W and
$-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to NH and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

and pharmaceutically acceptable salts thereof;

with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;

B. when R^1 is phenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, *p* is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;

C. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;

D. when R^1 is 4-chlorobenzoyl-CH_2-, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

E. when R^1 is 2-phenylphenyl, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

F. when R^1 is $CH_3OC(O)CH_2-$, R^2 is $-CH_3$, Z′ is $-CH_2-$, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

APPENDIX B

G. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $CH_3OC(O)CH_2$-, 4-$HOCH_2$-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S-, R^2 is -CH_3, Z′ is -CH_2-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

H. when R^1 is 2,6-difluorophenyl, R^2 is -CH_3, Z′ is -CH(OH)-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when the ring defined by W and -$C(H)_pC(=X)$- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

CYCLOALKYL, LACTAM, LACTONE AND RELATED COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, AND METHODS FOR INHIBITING β-AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/064,851 which was converted pursuant to 37 C.F.R. § 1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025, filed December 23, 1996.

Field of the Invention

This invention relates to compounds which inhibit β-amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease.

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All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type

(HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the β-amyloid peptide (βAP) or sometimes Aβ, AβP or β/A4. β-Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.[1] The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829[2].

Molecular biological and protein chemical analyses have shown that the β-amyloid peptide is a small fragment of a much larger precursor protein termed the amyloid precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding APP has demonstrated that β-amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the β-amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the cerebral and meningeal blood vessels is currently unknown.

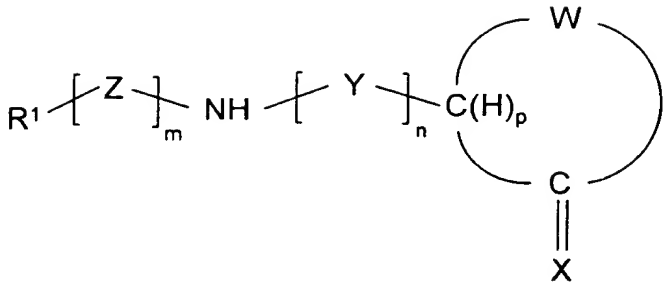
Several lines of evidence indicate that progressive cerebral deposition of β-amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe[3]. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with

a genetically determined (familial) form of AD (Goate, et al.[4]; Chartier Harlan, et al.[5]; and Murrell, et al.[6]) and is referred to as the Swedish variant. A double mutation changing lysine^{595}-methionine^{596} to asparagine^{595}-leucine^{596} (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.[7]). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the β-amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino acid 692 appears to cause a phenotype that resembles AD is some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its β-amyloid peptide fragment can cause AD.

Despite the progress which has been made in understanding the underlying mechanisms of AD and other β-amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting β-amyloid peptide release and/or its synthesis *in vivo*.

SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of compounds which inhibit β-amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of AD in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The class of compounds having the described properties are defined by formula I below:



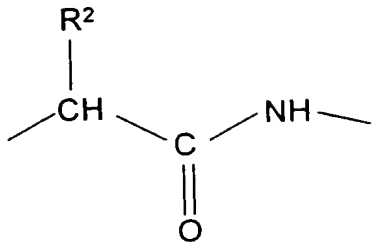
I

wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

X is selected from the group consisting of oxo (=O), thiooxo (=S), hydroxyl (-H, -OH), thiol (H,-SH) and hydro (H,H);

Y is represented by the formula:



wherein each R^2 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

Z is represented by the formula -T-CX′X″C(O)- where T is selected from the group consisting of a bond covalently linking R^1 to -CX′X″-, oxygen, sulfur, $-NR^5$ where R^5 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

X′ is hydrogen, hydroxy or fluoro,

X″ is hydrogen, hydroxy or fluoro, or X′ and X″ together form an oxo group;

m is an integer equal to 0 or 1;

n is an integer equal to 0, 1 or 2;

p is an integer equal to 0 or 1 such that when *p* is zero, the ring defined by W and $-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to Y and when *p* is one, the ring is saturated at the carbon atom of ring attachment to Y,

with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;

B. when R^1 is phenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form a trans-2-hydroxy-cyclohex-1-yl group;

C. when R^1 is phenyl, Z is $-CH_2C(O)-$, *m* is 1, *n* is 0, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form a gamma-butyrolactone group or a 5,5-dimethyl-gamma-butyrolactone group;

D. when R^1 is phenyl, Z is $-CH_2C(O)-$, *m* is 1, *n* is 0, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form a ϵ-caprolactam group;

E. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form an N-methylcaprolactam group;

F. when R^1 is 4-chlorobenzoyl-CH_2-, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

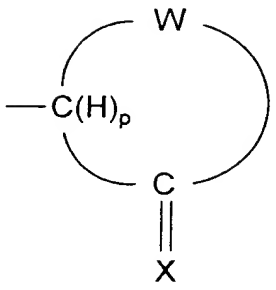
G. when R^1 is 2-phenylphenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

H. when R^1 is $CH_3OC(O)CH_2-$, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $CH_3OC(O)CH_2-$, 4-$HOCH_2$-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S-, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form a 2,3-dihydro-1-(*N,N*-diethylamino-CH_2CH^2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

J. when R^1 is 2,6-difluorophenyl, R^2 is $-CH_3$, Z is $-CH(OH)C(O)-$, *m* is 1, *n* is 1, and *p* is 1, then W, together with $>CH$ and $>C=X$, does not form a 2,3-dihydro-1-(*N,N*-diethylamino-CH_2CH^2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one,

K. when *m* is 1 and *n* is 1, then



does not equal cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

Accordingly, in one of its method aspects, this invention is directed to a method for inhibiting β-amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds of formula I above effective in inhibiting the cellular release and/or synthesis of β-amyloid peptide.

Because the *in vivo* generation of β-amyloid peptide is associated with the pathogenesis of AD[8,9], the compounds of formula I can also be employed in conjunction with a pharmaceutical composition to prophylactically and/or therapeutically prevent and/or treat AD. Accordingly, in another of its method aspects, this invention is directed to a prophylactic method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

Example Bio-1

Cellular Screen for the Detection of Inhibitors of β-Amyloid Production

Numerous compounds of formula I above were assayed for their ability to inhibit β-amyloid production in a cell line possessing the Swedish mutation. This screening assay employed cells (K293 = human kidney cell line) which were stably transfected with the gene for amyloid precursor protein 751 (APP751) containing the double mutation $Lys_{651}Met_{652}$ to $Asn_{651}Leu_{652}$ (APP751 numbering) in the manner described in International Patent Application Publication No. 94/10569[8] and Citron et al.[12]. This mutation is commonly called the Swedish mutation and the cells, designated as "293 751 SWE", were plated in Corning 96-well plates at 2-4 x 10^4 cells per well in Dulbecco's minimal essential media (Sigma, St. Louis, MO) plus 10% fetal bovine serum. Cell number is important in order to achieve β-amyloid ELISA results within the linear range of the assay (~0.2 to 2.5 ng per mL).

Following overnight incubation at 37°C in an incubator equilibrated with 10% carbon dioxide, media were removed and replaced with 200 μL of a compound of formula I (drug) containing media per well for a two hour pretreatment period and cells were incubated as above. Drug stocks were prepared in 100% dimethyl sulfoxide such that at the final drug concentration used in the treatment, the concentration of dimethyl sulfoxide did not exceed 0.5% and, in fact, usually equaled 0.1%.

At the end of the pretreatment period, the media were again removed and replaced with fresh drug containing media as above and cells were incubated for an additional two hours. After treatment, plates were centrifuged in a Beckman GPR at 1200 rpm for five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, 100 μL of conditioned media or appropriate dilutions thereof were transferred into an ELISA plate precoated with antibody 266 [P. Seubert, *Nature* (1992) **359**:325-327] against amino acids 13-28 of β-amyloid peptide as described in International Patent Application

Publication No. 94/10569[8] and stored at 4°C overnight. An ELISA assay employing labelled antibody 3D6 [P. Seubert, *Nature* (1992) **359**:325-327] against amino acids 1-5 of β-amyloid peptide was run the next day to measure the amount of β-amyloid peptide produced.

Cytotoxic effects of the compounds were measured by a modification of the method of Hansen, et al.[13]. To the cells remaining in the tissue culture plate was added 25 μL of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, St. Louis, MO) stock solution (5 mg/mL) to a final concentration of 1 mg/mL. Cells were incubated at 37°C for one hour, and cellular activity was stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylsulfate in 50% dimethylformamide, pH 4.7). Complete extraction was achieved by overnight shaking at room temperature. The difference in the OD_{562nm} and the OD_{650nm} was measured in a Molecular Device's UV_{max} microplate reader as an indicator of the cellular viability.

The results of the β-amyloid peptide ELISA were fit to a standard curve and expressed as ng/mL β-amyloid peptide. In order to normalize for cytotoxicity, these results were divided by the MTT results and expressed as a percentage of the results from a drug free control. All results are the mean and standard deviation of at least six replicate assays.

The test compounds were assayed for β-amyloid peptide production inhibition activity in cells using this assay. The results of this assay demonstrate that the compounds of formula I inhibit β-amyloid peptide production by at least 30% as compared to control.

Example Bio-2

***In Vivo* Suppression of β-Amyloid Release and/or Synthesis**

This example illustrates how the compounds of this invention could be tested for *in vivo* suppression of β-amyloid release and/or synthesis. For these

experiments, 3 to 4 month old PDAPP mice are used [Games et al., (1995) *Nature* 373:523-527]. Depending upon which compound is being tested, the compound is usually formulated at between 1 and 10 mg/mL. Because of the low solubility factors of the compounds, they may be formulated with various vehicles, such as corn oil (Safeway, South San Francisco, CA); 10% ethanol in corn oil; 2-hydroxypropyl-β-cyclodextrin (Research Biochemicals International, Natick MA); and carboxy-methyl-cellulose (Sigma Chemical Co., St. Louis MO).

The mice are dosed subcutaneously with a 26 gauge needle and 3 hours later the animals are euthanized via CO_2 narcosis and blood is taken by cardiac puncture using a 1 cc 25G 5/8" tuberculin syringe/needle coated with solution of 0.5 M EDTA, pH 8.0. The blood is placed in a Becton-Dickinson vacutainer tube containing EDTA and spun down for 15 minutes at 1500 xg at 5°C. The brains of the mice are then removed and the cortex and hippocampus are dissected out and placed on ice.

1. Brain Assay

To prepare hippocampal and cortical tissue for enzyme-linked immunosorbent assays (ELISAs) each brain region is homogenized in 10 volumes of ice cold guanidine buffer (5.0 M guanidine-HCl, 50 mM Tris-HCl, pH 8.0) using a Kontes motorized pestle (Fisher, Pittsburgh PA). The homogenates are gently rocked on a rotating platform for three to four hours at room temperature and stored at -20°C prior to quantitation of β-amyloid.

The brain homogenates are diluted 1:10 with ice-cold casein buffer [0.25% casein, phosphate buffered saline (PBS), 0.05% sodium azide, 20 µg/ml aprotinin, 5 mM EDTA, pH 8.0, 10 µg/ml leupeptin], thereby reducing the final concentration of guanidine to 0.5 M, before centrifugation at 16,000 xg for 20 minutes at 4°C. Samples are further diluted, if necessary, to achieve an optimal range for the ELISA measurements by the addition of casein buffer with 0.5 M

guanidine hydrochloride added. The β-amyloid standards (1-40 or 1-42 amino acids) were prepared such that the final composition equaled 0.5 M guanidine in the presence of 0.1% bovine serum albumin (BSA).

The total β-amyloid sandwich ELISA, quantitating both β-amyloid (aa 1-40) and β-amyloid (aa 1-42) consists of two monoclonal antibodies (mAb) to β-amyloid. The capture antibody, 266 [P. Seubert, *Nature* (1992) **359**:325-327], is specific to amino acids 13 - 28 of β-amyloid. The antibody 3D6 [Johnson-Wood et al., *PNAS USA* (1997) **94**:1550-1555], which is specific to amino acids 1 - 5 of β-amyloid, is biotinylated and served as the reporter antibody in the assay. The 3D6 biotinylation procedure employs the manufacturer's (Pierce, Rockford IL) protocol for NHS-biotin labeling of immunoglobulins except that 100 mM sodium bicarbonate, pH 8.5 buffer is used. The 3D6 antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP but detects only β-amyloid species with an amino terminal aspartic acid. The assay has a lower limit of sensitivity of ~50 pg/ml (11 pM) and shows no cross-reactivity to the endogenous murine β-amyloid peptide at concentrations up to 1 ng/ml.

The configuration of the sandwich ELISA quantitating the level of β-amyloid (aa 1-42) employs the mAb 21F12 [Johnson-Wood et al., *PNAS USA* (1997) **94**:1550-1555] (which recognizes amino acids 33-42 of β-amyloid) as the capture antibody. Biotinylated 3D6 is also the reporter antibody in this assay which has a lower limit of sensitivity of ~125 pg/ml (28 pM).

The 266 and 21F12 capture mAbs are coated at 10 μg/ml into 96 well immunoassay plates (Costar, Cambidge MA) overnight at room temperature. The plates are then aspirated and blocked with 0.25% human serum albumin in PBS buffer for at least 1 hour at room temperature, then stored desiccated at 4°C until use. The plates are rehydrated with wash buffer (Tris-buffered saline, 0.05% Tween 20) prior to use. The samples and standards are added to the

plates and incubated overnight at 4°C. The plates are washed ≥ 3 times with wash buffer between each step of the assay. The biotinylated 3D6, diluted to 0.5 μg/ml in casein incubation buffer (0.25% casein, PBS, 0.05% Tween 20, pH 7.4) is incubated in the well for 1 hour at room temperature. Avidin-HRP (Vector, Burlingame CA) diluted 1:4000 in casein incubation buffer is added to the wells for 1 hour at room temperature. The colorimetric substrate, Slow TMB-ELISA (Pierce, Cambridge MA), is added and allowed to react for 15 minutes, after which the enzymatic reaction is stopped with addition of 2 N H_2SO_4. Reaction product is quantified using a Molecular Devices Vmax (Molecular Devices, Menlo Park CA) measuring the difference in absorbance at 450 nm and 650 nm.

2. Blood Assay

The EDTA plasma is diluted 1:1 in specimen diluent (0.2 gm/l sodium phosphate•H_2O (monobasic), 2.16 gm/l sodium phosphate•$7H_2O$ (dibasic), 0.5gm/l thimerosal, 8.5 gm/l sodium chloride, 0.5 ml Triton X-405, 6.0 g/l globulin-free bovine serum albumin; and water). The samples and standards in specimen diluent are assayed using the total β-amyloid assay (266 capture/3D6 reporter) described above for the brain assay except the specimen diluent was used instead of the casein diluents described.

Formulations other than those described above can also be used for oral delivery and intravenous delivery to a mammal. For oral delivery, the compound can be mixed with either 100% corn oil or, alternatively, in a solution comtaining 80% corn oil, 19.5% oleic acid and 0.5% labrafil. The compound can be mixed with the above solutions in concentrations ranging from 1 mg/mL to 10 mg/mL. The compound in solution is preferably administered orally to the mammal at a dose volume of 5 mL/kg of body weight. For IV delivery, the compound is preferably mixed with a solution of 3% ethanol, 3% solutol HS-15 and 94% saline. The compound is preferably mixed with the above solution in concentrations ranging from 0.25 mg/mL to 5 mg/mL. The

compound in solution is preferably administered by IV to the mammal at a dose volume of 2 mL/kg of body weight.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

Patent
Attorney's Docket No. 002010-586

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Jing WU et al.	Group Art Unit: Unassigned
Application No.: Unassigned (Div. of 08/996,422)	Examiner: Unassigned
Filed: Herewith	
For: CYCLOALKYL, LACTAM, LACTONE AND RELATED COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, AND METHOD FOR INHIBITING β-AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS	

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits and calculation of fees, please amend the above-identified application as follows:

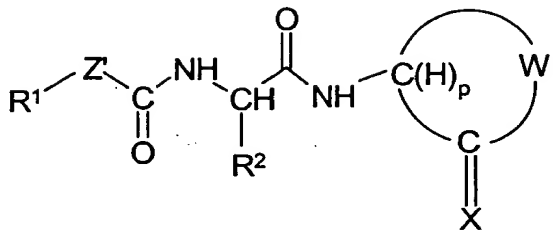
IN THE SPECIFICATION:

Please replace the first paragraph of page 1 appearing under the section "Cross-Reference to Related Applications" with the following paragraph:

-- This application is a division of U.S. Application Serial No. 08/996,422 filed December 22, 1997, which claims priority under 35 U.S.C. §119(e) from U.S. Provisional Application No. 60/064,851 which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025 filed December 23, 1996.--

Please insert the following paragraphs between the third and fourth full paragraphs on page 14, line 27 insert:

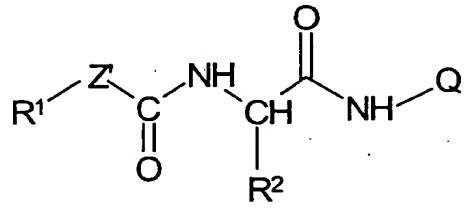
-- The compounds of formula I wherein m is 1 and n is 1can be represented by the following formula:



IA

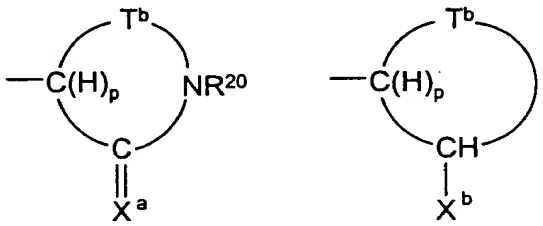
wherein R^1, R^2, W, X and *p* are as defined hereinabove with respect to formula I and Z′ is represented by the formula -CX′X″-, -T-CH_2- or -T-C(O)- where T is selected from the group consisting oxygen, sulfur, -NR^5 where R^5 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X′ is hydrogen, hydroxy or fluoro; X″ is hydrogen, hydroxy or fluoro, or X′ and X″ together form an oxo group.

A further grouping of compounds within the invention can be represented by the following formula IB:



IB

wherein R^1 and R^2 are defined hereinabove with respect to formula I, Z′is defined hereinabove with respect to formula IA, and Q is selected from the group of monocyclic and polycyclic groups having the formulas:



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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,440	07/30/2001	Jing Wu	002010-586	2003

21839 7590 12/20/2002

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	13

DATE MAILED: 12/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Elan Pharmaceutical
002010-586
GES/DMM/EMD
Final Rejection
Resp Due 3/20/03

Office Action Summary

Application No.	Applicant(s)
09/916,440	Wu et al.
Examiner	**Art Unit**
Bruck Kifle, Ph.D.	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 7, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *91-145* is/are pending in the application.

4a) Of the above, claim(s) *96-103, 105-108, 123-130, and 132-135* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *91-95, 104, 109-122, 131, and 136-145* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

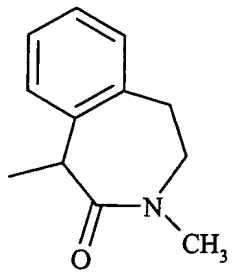
15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3, 9, 10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's amendments and remarks filed 10/7/02 have been received and reviewed. Claims 91-145 are pending in this application.

Applicants are advised that only the elected subject matter is under consideration. That is, compounds and pharmaceutical compositions, wherein W, together with $-C(H)_pC(=X)$, and Q form the ring system



is under consideration.

Claims 96-103, 105-108, 123-130 and 132-135 along with subject matter not embraced by this ring system of the remaining claims are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter. Election was made without traverse in Paper No. 6.

Applicants are advised that this application still contains non-elected subject matter in the claims. Note, the court in In re Herrick et al and In re Joyce (both at 115 USPQ 412) held that an election of species requirement was, in fact, a restriction requirement.

Improper Markush Rejection

Claims 91-95, 104, 109-122, 131 and 136-145 are again rejected as being drawn to an improper Markush group, that is, the claims lack unity of invention. The basis of this rejection is

the same as given in the previous office action and is incorporated herein fully by reference. Applicants argue that the Examiner did not consider the compound as a whole. However, the compounds were in fact considered as whole and determined that their inclusion in a common group is repugnant to principles of scientific classification. In re Harnish restricted the applicant to one core, and indicated in footnote 7, thereof, that a restriction and rejection based on a reference for one ring not being a reference for another was authorized (206 USPQ 300 at 305 and 306). Footnote 7 of Harnish says "having recognized the possibility of rejecting a Markush group on the basis of independent and distinct inventions" in that a reference for one would not be a reference for the other.

Limiting the claims to compounds wherein W, together with $-C(H)_pC(=X)$, and Q form the elected ring system (the benzoazepinone ring) would overcome this rejection.

Claim 145 has 68 pages of compounds, about 800 species. This number of compounds cannot be considered "a reasonable number" according to rule 1.140(a). MPEP rule 1.141(a) is again reproduced below.

§ 1.141 Different inventions in one national application.

(a) Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form (1.75) or otherwise include all the limitations of the generic claim.

Applicants argue that the instant application contains one invention. However, this is not persuasive. First, there was an election of species requirement where Applicants were required to elect a single disclosed species because the claims are drawn to patentably distinct species. Applicants were also advised that should they traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention. Applicants elected a species without traverse.

Secondly, the number of species claimed in claim 145 is not reasonable. Applicants paid, at most, $80 for this claim. The cost to search each species is $45 on the CAS database. Each species has to be searched separately. In re Fressola, 22 USPQ 2nd 1828, indicates that the Examiner may reject for Applicants failure to follow a Rule. Claim 145 is an aggravated example of ultimate species listed in a claim as to avoid fees. The claim is not a Markush claim.

Claim 145 is rejected as failing to comply with 37 CFR 1.141(a).

Applicants are again requested to read the rule and write the claim in dependent form where there is a generic claim present that embraces all of the species in the claim and limit the number of species to a reasonable number of species per claim.

Provisos

There are provisos in the claims that exclude compounds embraced by the claims. If these provisos are present to avoid prior art, applicants are urgently requested to point out these references to the examiner because of their importance in the examination of the claims. Applicants did not respond to this query.

The search revealed that the elected compound is disclosed in several of Applicants pending applications. See for example WO 99/67221 and WO 98/28268. Also, WO 2001/034571 overlaps generically. Applicants are required to maintain a clear line of demarcation between the applications. See MPEP § 822. Applicants have not indicated what the differences are.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

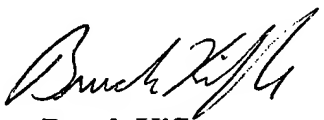
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle whose telephone number is (703) 305-4484.

The fax phone number for this Group is (703) 308-4556 or (703) 305-3592. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

December 18, 2002



Bruck Kifle
Primary Examiner
Art Unit 1624

#

SHEET 1 OF 1

Substitute for form 1449A/PTO	ATTORNEY'S DKT NO. 002010-586	APPLICATION NO. 09/916,440
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	APPLICANT Jing Wu, t al.	
	FILING DATE July 30, 2001	GROUP 1624

U.S. PATENT DOCUMENTS

Examiner Initials	Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)
B.K.	3,657,341		Thorne, et al. 260/558	4/18/72
	4,410,520		Watthey 424/244	10/18/83
	4,473,575		Watthey 424/203	9/25/84
	5,015,639		Berger et al. 514/213	5/14/91
	5,206,235		Fisher et al. 514/213	4/27/93
	5,247,080		Berger et al. 540/523	9/21/93
	5,486,541		Sterling et al. 514/657	1/23/96
	5,502,048		Chapdelaine et al. 514/213	3/26/96
	5,519,061		Youdim et al. 514/647	5/21/96
	5,532,415		Youdim et al. 564/308	7/2/96
	5,656,626		Chapdelaine et al. 514/213	8/12/97
	5,672,598		De et al. 514/212	9/30/97

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation no
B.K.	EP 0 732 399		Europe	9/18/96		
B.K.	GB 1 519 931		UK	1/6/77		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
B.K.	Semple, et al., "Design, Synthesis and Evolution of a Novel, Selective, and Orally Bioavailable Class of Thrombin Inhibitors: P1-Argininal Derivatives Incorporating P3-P4 Lactam Sulfonamides Moieties", *J. Med. Chem*, Vol. 39, pp. 4531-4536, (1996).

Examiner Signature	Bruce Kiffle	Date Considered	12/18/02

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO.	APPLICATION NO.
002010-586	09/916,440
APPLICANT: Jing Wu, et al.	
FILING DATE: July 30, 2001	GROUP: 1624

U.S. PATENT DOCUMENTS

Examiner Initials	U.S. Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)
B.K.	2,938,029		Brenner et al. 260/239.3	5/24/60
B.K.	3,598,859		Yates et al. 260/471	8/10/71
B.K.	4,080,449		Croisier et al. 424/244	3/21/78
B.K.	4,460,579		Karenewsky 424/200	7/17/84
B.K.	5,478,857		Clemens et al. 514/381	12/26/95
B.K.	5,658,901		Claremon et al. 514/221	8/19/97

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation no
B.K.	0 061 187		Europe	9/29/82		
	810221A		Europe			
	WO 92/16524		PCT	10/1/92		
	WO 95/25117		PCT	9/21/95		
	WO 96/25408		PCT	8/22/96		
	WO 96/29313		PCT	9/26/96		
	WO 97/38705		PCT	10/23/97		
	WO 97/16410		PCT	5/9/97		
	WO 98/04539		PCT			
	WO 98/22494		PCT	5/28/98		
	WO 98/22430		PCT	5/28/98		
	WO 98/22433		PCT	5/28/98		
	WO 98/22494		PCT	5/28/98		
	WO 98/38177		PCT	9/3/98		
	GB 1,519,495		UK	7/26/78		
	HU 71515		Hungary	12/28/95		
	JP 179757		Japan	4/21/98		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
B.K.	Akhatar, et al., "Bicyclic Imides with Bridgehead Nitrogen..", *J. Org. Chem.*, 55: pp. 5222-5225 (1990).
B.K.	Armstrong, et al., "An Efficient Asymmetric Synthesis of (R)-3-Amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one", *Tetrahedron Letters*, 35: pp. 3239-3242 (1994).

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO.	APPLICATION NO.
002010-586	09/916,440
APPLICANT	
Jing Wu, et al.	
FILING DATE	GROUP
July 30, 2001	1624

B.K.	Barton, et al., "A New Rearrangement of Ketonic Nitrones...", *J. Chem. Soc.*, pp. 1764-1767 (1975).
	Ben-Ishai, et a., "Intra vs Intermolecular Amidoalkylation of Aromatics", *Tetrahedron*, 43:2, pp. 439-450 (1987).
	Blade-Font,"Facile Synthesis of γ-,δ-, and ϵ-lactams by Cyclodehydration of ω-amino Acids on Alumina or Silica Gel", *Tetrahedron Letters*, 21: 2443-2446 (1980).
	Brown, et al., "A Revision of the Structure of "7-Phenyloxindole", *Tetrahedron Letters*, 8: pp. 667-670 (1971).
	Burkholder, et al., "The Synthesis of 6-Amino-5-Oxo-7-Phenyl-1,4-Oxazepines As Conformationally Constrained *Cauche* (-) Dipeptide Mimetics", *Biog. Med. Chem. Letter*, 2: p. 231 (1993)
	Busacca, et al., "Synthesis of Novel Tetrahydrobenzazepinones", *Tetrahedron Letters*, 33:2, pp. 165-168 (1992).
	Butcher, et al., "Preparation of 3-Amino-1,4-Benzodiazepin-2-Ones Via Direct Azidation with Trisyl Azide", *Tetrahedron Letters*, 37:37, pp. 6685-6688 (1996).
	Chartier-Harlin, et al., "Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-Amyloid precursor protein gene.", *Nature*. 353:31, pp. 844-846 (1991).
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO.	APPLICATION NO.
002010-586	09/916,440
APPLICANT: Jing Wu, et al.	
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O.K.	Dickerman, et al., "Studies in Piperdidone Chemisty", *J. Org. Chem.*, 14, p. 530-536 (1949).
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APPLICANT	
Jing Wu, t al.	
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D.K.		Hoffman, et al., "Efficient Synthesis of N-Substituted Lactams from (N-Arylsulfonyloxy) Amines and Cyclic Ketones", *Tetrahedron Letters*, 30: pp. 4207-4210 (1989).
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B.K.	Lowe, et al., "5,7-Diphenyl-3-Ureidohexahydroazepin-2-Ones as Cholecystokinin-B Receptor Ligands", *Bioorg & Med Chem Letters*, 4:24, pp. 2877-2882 (1994).
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BK		Sekakida, et al., "Studies on Seven-membered Heterocyclic Compounds Containing Nitrogen", *Bull. Chem. Soc. Japan*, 44: pp. 478-480 (1971).
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B.K.	Wheeler, et al., "Formation and Photochemical Wolff Rearrangement of Cyclic α-Diazo Ketones", *Organic Syntheses*, Coll. Vol. VI, p. 840.
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Examiner Signature	Date Considered
Bruce Kisliuk	12/18/02

#10

SHEET 1 OF 1

Substitute for form 1449A/PTO	ATTORNEY'S DKT NO.	APPLICATION NO.
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	APPLICANT: Jing Wu, t al.	
	FILING DATE: July 30, 2001	GROUP: 1624

U.S. PATENT DOCUMENTS

Examiner Initials	U.S. Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation no
B.K.	0591529		Europe	4/13/94		
	0647632		Europe	4/12/95		
	0945445		Europe	9/29/99		
	WO 92/11246		PCT	7/9/92		
	WO 94/00438		PCT	1/6/94		
	WO 94/25445		PCT	11/10/94		
	WO 95/03285		PCT	2/2/95		-
	WO 98/25911		PCT	6/18/98		
	5247033		Japan	9/24/93		
	6211812		Japan	8/2/94		
✓	10101560		Japan	4/21/98		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.

Examiner Signature	Date Considered
Bruce Kyle	12/18/02

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,440	07/30/2001	Jing Wu	002010-586	2003

21839 7590 04/05/2002

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EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	7

DATE MAILED: 04/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Elan Pharmaceuticals, Inc.
GRS | LSS
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C.C.
4/8

Response due
7/5/02
4/11 → GPS

Office Action Summary	Application No. 09/916,440	Applicant(s) Wu et al.
	Examiner Bruck Kifle, Ph.D.	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *91-145* is/are pending in the application.

4a) Of the above, claim(s) *96-103, 105-108, 123-130, and 132-135* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *91-95, 104, 109-122, 131, and 136-145* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1 and 4*

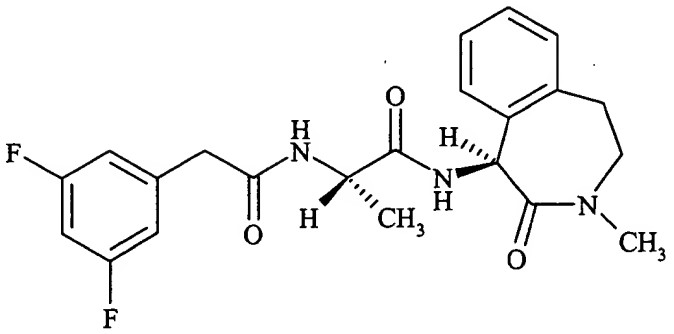
18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

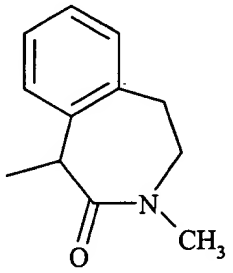
20) ☐ Other:

Election/Restriction

Applicant's election without traverse of the compound depicted below in Paper No. 6 is acknowledged.



The search was conducted to embrace compounds wherein W, together with -$C(H)_pC(=X)$, and Q form the ring system:



Claims 96-103, 105-108, 123-130 and 132-135 along with subject matter not embraced by this ring system of the remaining claims are withdrawn from consideration as being drawn to non-elected subject matter.

Improper Markush Rejection

Claims 91-95, 104, 109-122, 131 and 136-145 are rejected under a judicially created doctrine as being drawn to an improper Markush group, that is, the claims lack unity of invention. The ring formed by W, together with -$C(H)_pC(=X)$, and Q are defined in such a way

that they keep changing the core of the compound that determines the classification. By changing these values, several patentably distinct and independent compounds are claimed. In order to have unity of invention the compounds must have "a community of chemical or physical characteristics" which justify their inclusion in a common group, and that such inclusion is not repugnant to principles of scientific classification" In re JONES (CCPA) 74 USPQ 149 (see footnote 2). The structural formula IA and IB do not have a significant structural feature that is shared by all of its alternatives which is inventive. The structural formula IA and IB only have the -C(O)-NH-CH(R^2)-C(O)-NH- fragment as common. Compounds embraced by formula IA and IB are so diverse in nature that a prior art anticipating a claim with respect to one member under 35 USC 102 would not render obvious the same claim under 35 USC 103. This is evidentiary of patentably distinct and independent inventions.

Limiting the claims to compounds wherein W, together with -C(H)$_p$C(=X), and Q form the elected ring system (the benzoazepinone ring) would overcome this rejection.

Claim Rejections - 35 USC § 112

Claims 91-95, 104, 109-122, 131 and 136-145 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) In the independent claims the terms substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkenyl are present. The term "substituted" without saying which substituents

are intended is indefinite. One skilled in the art cannot say which substituents are permitted and which ones are not.

ii) The term "cycloalkyl"is indefinite because it is not known how many atoms make up the ring and what kind of a ring is intended (monocyclic, bicyclic, spiro, fused, bridged, saturated, etc.).

iii) The term "heteroaryl" is indefinite because it is not known how many atoms are present, how many and what kind of heteroatoms are involved, what size ring is intended and how many rings are present.

iv) The term "heterocyclic" is indefinite because it is not known how many atoms make up the ring, which atoms are present and what kind of a ring (monocyclic, bicyclic, spiro, fused, bridged, saturated, etc.) is intended.

v) The independent claims end with the phrase "and pharmaceutically acceptable salts thereof." This is improper Markush language because it is not in the alternative form. The term "or" is suggested in place of "and".

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely

exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the independent claims recite the broad recitations "optionally substituted heteroaryl" and "substituted alkyl" , and the claims also recite "2-aminopyrid-6-yl" and "-$(CH_2)_4NHC(O)OC(CH_3)_3$" which is the narrower statement of the range/limitation.

Applicants are reminded that although the claims are interpreted in light of the specification, critical limitations from the specification cannot be read into the claims (see, e.g., In re Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991)). Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention.

Claim 145 has 68 pages of compounds. This number of compounds cannot be considered "a reasonable number" according to rule 1.140(a). See also MPEP rule 1.141(a) reproduced below.

§ 1.141 Different inventions in one national application.

(a) Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form (1.75) or otherwise include all the limitations of the generic claim.

Provisos

There are provisos in the claims that exclude compounds embraced by the claims. If these provisos are present to avoid prior art, applicants are urgently requested to point out these references to the examiner because of their importance in the examination of the claims.

The search revealed that the elected compound is disclosed in several of Applicants pending applications. See for example WO 9/67221 and WO 98/28268. Also, WO 2001/034571 overlaps generically. Applicants are required to maintain a clear line of demarcation between the applications. See MPEP § 822.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle whose telephone number is (703) 305-4484.

The fax phone number for this Group is (703) 308-4556 or (703) 305-3592. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

April 4, 2002

Bruck Kifle
Primary Examiner
Art Unit 1624

#3

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO. 002010-586	APPLICATION NO. 09/916,440
APPLICANT Jing Wu, et al.	
FILING DATE July 30, 2001	Group 1624

U.S. PATENT DOCUMENTS

Examiner Initials	U.S. Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)
B.K.	4,410,520		Watthey 424/244	10/18/83
	4,473,575		Watthey 424/263	9/24/84
	5,015,639		Berger et al. 514/213	5/14/91
	5,206,235		Fisher et al. 514/213	4/27/93
	5,247,080		Berger et al. 540/523	9/21/93
	5,486,541		Sterling et al. 514/657	1/23/96
	5,502,048		Chapdelaire et al. 514/213	3/26/96
	5,519,061		Youdim et al. 514/467	5/21/96
	5,532,415		Youdim et al. 564/308	7/2/96
	5,656,626		Chapdelaine et al. 514/213	8/12/97
	5,672,598		De et al. 514/212	9/30/97

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation no

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.

Examiner Signature	Date Considered
Bruck K[illegible]	4/4/02

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered...

#1

INFORMATION DISCLOSURE CITATION

PTO-1449

ATTORNEY'S DKT NO.	APPLICATION NO.
002010-586	~~Unassigned~~ 09/916,442
APPLICANT: Jing Wu, et al.	
FILING DATE: ~~Filed Herewith~~ 7/30/01	GROUP: ~~Unassigned~~ 1624

U.S. PATENT DOCUMENTS

EXAMINER'S INITIALS	PATENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE
B.K.	3,657,341	4/18/72	Thorne, et al.	260	558	
	4,080,449	3/21/78	Croissier, et al.	424	244	
	4,477,464	10/16/84	Slade, et al.	424	275	
	4,666,829	5/19/87	Glenner, et al.	435	6	
	4,977,168	12/11/90	Bernat, et al.	514	330	
	5,238,932	8/24/93	Flynn, et al.	514	214	
	5,283,241	2/1/94	Bochis, et al.	514	183	
	5,284,841	2/8/94	Chu, et al.	514	183	
	5,324,726	6/28/94	Bock, et al.	514	221	
	5,360,802	11/1/94	Chambers, et al.	514	221	
	5,420,271	5/30/95	Warchawsky, et al.	540	521	
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	5,633,251	5/27/97	Claremon, et al.	514	221	
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	5,712,397	1/27/98	Esser, et al.	546	90	
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FILING DATE: jc997 U.S. PTO 09/916440 07/30/01

FOREIGN PATENT DOCUMENTS

EXAMINER'S INITIALS	PATENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	Translation Yes	Translation No
B.K.	1 063 108	9/25/79	Canada				
	0 167 919	1/15/86	Europe				
	0 284 256	9/28/88	Europe				
	0 349 949	1/10/90	Europe				

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O.K.	0 376 849	7/4/90	Europe				
	0 434 360	6/26/91	Europe				
	0 434 364	6/26/91	Europe				
	0 434 369	6/26/91	Europe				
	0 490 590	6/17/92	Europe				
	0 514 133	11/19/92	Europe				
	0 523 845	1/20/93	Europe				
	0 549 039	6/30/93	Europe				
	0 647 632	4/12/95	Europe				
	0 652 009	6/10/95	Europe				
	0 667 344	8/16/95	Europe				
	0 677 517	10/18/95	Europe				
	0 732 399	9/18/96	Europe				
	0 778 266	11/6/97	Europe				
	1 519 931	7/6/78	Great Britain				
	1 573 931	8/18/80	Great Britain				
	2 272 439	5/18/94	Great Britain				
	2 290 788	1/10/96	Great Britain				
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B.K.	95/03289	2/2/95	WIPO				
	95/03290	2/2/90	WIPO				
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	95/21840	8/17/95	WIPO				
	95/23810	9/8/95	WIPO				
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B.K.	Arienti, et al. "Regioselective Electrophilic Alkylation of Anilines with Phanylacetrylene in the Presence of Montmorillonite KSF." *Tetrahedron* 53(10): 3795-3804 (1997).
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B.K.	Reiter, et al. "Crystallization-Induced Asymmetric Transformation: Stereospecific Synthesis of a Potent Peripheral CCK Antagonist." *J. Org. Chem.* 52: 955-957 (1987).
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EXAMINER	DATE CONSIDERED
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.